PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does enhanced physical rehabilitation following intensive care unit discharge improve outcomes in patients who received mechanical ventilation? A systematic review and meta-analysis
AUTHORS	Taito, Shunsuke; Yamauchi, Kota; Tsujimoto, Yasushi; Banno, Masahiro; Tsujimoto, Hiraku; Kataoka, Yuki

VERSION 1 - REVIEW

REVIEWER	Rebecca Cusack University Hospital of Southampton NHS FT UK
REVIEW RETURNED	19-Oct-2018

GENERAL COMMENTS	●The conclusion of the abstract states ' Implementing an intensive physical rehabilitation program for all ICU survivors requiring mechanical ventilation is unnecessary' - this does not answer the question ' does enhanced physical rehabilitation following ICU discharge improve clinically relevant outcomes...' ● long term mortality described yet none of the studies had follow-up beyond 6 months and most of the studies examined were not powered to examine mortality ●QoL physical mental components- do not add information above what is described in 2015 (pg 58) ● the definition of enhanced physical rehabilitation (148-54) in many countries encompasses a normal rehabilitation pathway for all patients ● meta analysis described as first to focus on enhanced rehabilitation.....in which the study intervention was conducted only after ICU discharge however - half of the studies had rehabilitation within ICU before randomisation ● (292-4) ...'results ..... suggest that enhanced rehabilitation following ICU discharge could not improved QoL....' again a generalised conclusion for very limited data ● (-305-7) unjustified conclusions -insufficient data , poor quality ●(311-314) - early rehabilitation in other conditions has is some studies resulted in detrimental - it is can not be assumed transfer such conclusion to completely different cohorts is appropriate and the danger of doing this is not mentioned ●(317-9) this review does not examine resource use or recuperation and therefore no conclusions can be taken form the analysis performed ● ? for statistician - is sub-group analysis appropriate

REVIEWER	Professor Stephen Brett Imperial College London UK None- other than I collaborate with some of the investigators in some of the studies included. I was trial steering group chair for the RECOVER study which is included.
REVIEW RETURNED	25-Nov-2018

GENERAL COMMENTS	This is a well presented and thorough manuscript. I have a few comments for consideration. For the conclusion that physical rehab to have no patient centred effect to be secure we have to be confident that the outcome measures are sensitive to change in this population and it is currently far from clear that this is the case- or that we really know hoe to do this. It is possible that the outcome measures are simply not sufficiently sophisticated enough- this should be acknowledged. Several studies- the RECOVER and the PIX studies- did not demonstrate an improvement in primary quantitative outcome- but did show evidence of benefit of the intervention in parallel qualitative evaluation. This somewhat supports my first point. From work that we have done with patient and family groups they tell us that patient motivation and engagement is fundamental to full participation in the intervention- thus single modality physical interventions which ignore psychological aspects are very unlikely to be beneficial at a population level- although highly self-motivated individuals may derive benefit. The authors very sensibly chose a random effects approach to deal with statistical heterogeneity- but at a trial level there was heterogeneity in almost everything. It would be reasonable for them to emphasise the heterogeneity of outcome measures hinders overall analysis here- and somewhat erodes the power of the meta-analysis. .

REVIEWER	Simon Baudouin Newcastle upon Tyne NHS Foundation Trust, United Kingdom
REVIEW RETURNED	26-Nov-2018

GENERAL COMMENTS	The authors present the results of both a systematic review and meta-analysis on the effect of post critical care discharge rehabilitation on outcome. This topic has been previously addressed but the authors justify their study by the inclusion of new RCTs published since the previous systematic review of Connelly et al. The study use standard Cochrane Collaboration methodology and appears well conducted. Pre-defined outcomes were chosen including Quality of life, ADL function and mortality. Comprehensive search strategies were employed supplemented by hand searching and in some cases personal contact with study authors. Search strategies are provided in one of the supplements. Study quality was assessed using standard risk of bias and GRADE assessment tools. Analysis was again standard using the Cochrane Review Manager software. Ten RCTs were included. Results were presented using Forest plots for the meta analysis and descriptive statistics where appropriate. The conclusions were similar to previous publications with no strong evidence in favour of post ITU intensive physical

	rehabilitation. A mention of the very heterogeneous nature of the critical care populations included should be made.

REVIEWER	Teresa Neeman Australian National University, Australia
REVIEW RETURNED	21-Dec-2018

GENERAL COMMENTS	1. Overall a well-written meta-analysis. 2. Mortality outcome: it is not clear what is meant by short-term and long-term mortality. Can you clarify this please? 30 days? 6 months? 1 year? 3. Also, for "long-term" mortality, journal articles often present hazard ratios, or log rank statistics and total number of deaths. Presenting RR for mortality suggests that the status of every patient is known at the time of assessment. This is rarely the case, as there is often a loss to follow-up (censoring) which must be accounted for. Could you please clarify your reasons for presenting long-term mortality effects in terms of RR? 4. Summary of findings: It would be clearer if the mortality endpoints had time durations, e.g. 30 day mortality or 1 year morality. Then the numbers (31 out of 1000) would be more meaningful to the reader. 5. This reviewer noted that 9 of the 10 included studies reported HRQoL as an outcome measure. I assume different QoL instruments were used, but I wonder why the authors combine the study QoL results using a standardised mean difference, as they planned (see Statistical Analysis section)?

VERSION 1 – AUTHOR RESPONSE

To reviewer #1

Thank you very much for the reviewer's thorough review of our manuscript. We have revised our manuscript according to the reviewer's suggestions. Our point-by-point responses to reviewer's comment are below.

●The conclusion of the abstract states ' Implementing an intensive physical rehabilitation program for all ICU survivors requiring mechanical ventilation is unnecessary' - this does not answer the question ' does enhanced physical rehabilitation following ICU discharge improve clinically relevant outcomes...'
Response: According to reviewer #1's suggestion, the Associate Editor's comment and reviewer #2's comment, we revised conclusion in abstract and discussion as below.

In abstract
Conclusions: Enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation. With regards to the wide CI, we believe further studies are needed to confirm the efficacy of rehabilitation.

On page 22, line 365-369 in discussion
Taken together, the findings of the present meta-analysis indicate that enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation. With regards to the wide CI, we believe further studies are needed to confirm the efficacy of rehabilitation.

● long term mortality described yet none of the studies had follow-up beyond 6 months and most of the studies examined were not powered to examine mortality
Response: We thank the reviewer of their comments. We described that we divided the timing for the measurements of the outcomes into the short-term (28-35 days) and the long-term (6 months) in pre-specified protocol (PROSPERO registry ID: CRD42017080532), thus we did not account for later outcomes. However, 2 studies [Cuthbertson BH, et al.; Walsh TS, et al] had follow-up periods beyond 6 months, and we performed additional analysis as below. Cuthbertson et al. reported that enhanced physical rehabilitation did not significantly improve SF-36 score at 12 months. Walsh et al. study also reported that enhanced physical rehabilitation did not significantly improve SF-12 score at 12 months. Regarding 12 months mortality, the enhance physical rehabilitation did not significantly improve 1-year mortality (RR: 1.16, 95%CI [0.70-1.93]).

According to the reviewer's suggestion, we have added these results and revised our results and discussion sections of our manuscript as below.

In results (on page 15 line 241-242, page 16-17 line 266-269)
Two studies [12, 23] had a follow-up >6 months.

We performed additional analysis regarding follow-up at 12 months, the SMD [95% CI] between the intervention and control groups regarding PCS and MCS scores was 0.03 [-0.18 to 0.24] and 0.00 [-0.12 to 0.31]. Enhanced physical rehabilitation also did not decrease mortality at 12 months (RR: 1.16, 95%CI [0.70-1.93]) (see detail provided in online supplementary file 6).

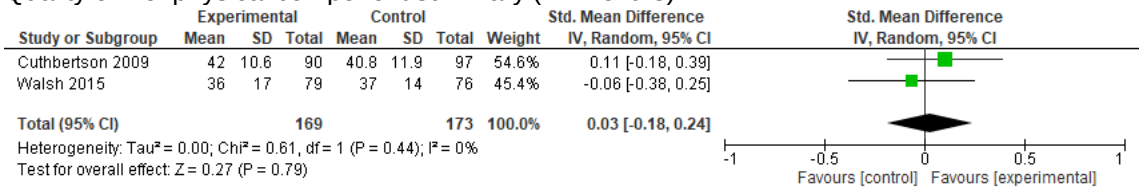
In the discussion (on page 18 line 296-299, on page 21 line 350-352,)
The results of this up-to-date review covering 10 RCTs and 1110 patients suggest that enhanced rehabilitation following ICU discharge might not improve QOL or reduce mortality among patients who received mechanical ventilation at the 6 or 12 month follow up.

Firstly, few studies [12, 23] had a follow-up >6 months, and we could not consider enough with a following up of greater than 6 months. Further studies and update review follow-up beyond 6 months will be needed.

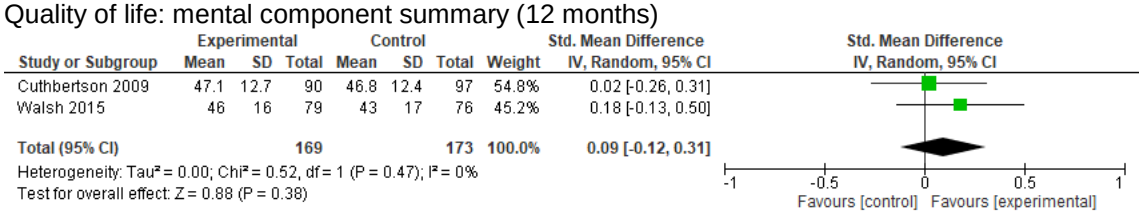
In addition, included studies did not examine the power for mortality as per the reviewer's comments, and these studies included some loss to follow-up. In 5 studies, the total loss to follow-up in the intervention group was 15.7% and in the control group was 13.6% (Jones 2003, Cuthbertson 2009, Elliot 2011, Walsh 2015, McDowell 2017). To consider attrition bias [Higgins et al.], we reassessed risk of bias and changed the domain of incomplete outcome data from low to high in online supplemental file 5. We also added this point to the results as below.

Results(page 15, line 249)
Five studies had high risk of incomplete outcome data.

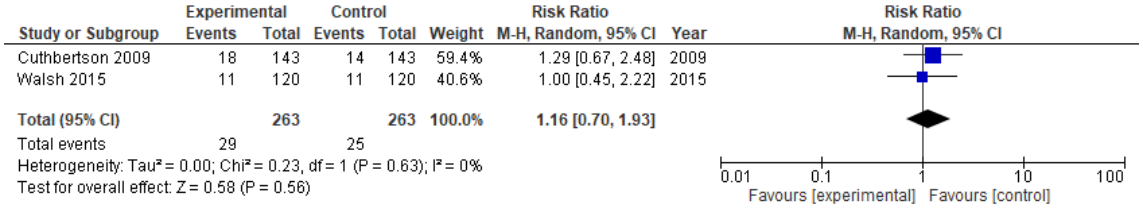
Quality of life: physical component summary (12 months)



Quality of life: mental component summary (12 months)



Mortality (12 months)



●QoL physical mental components- do not add information above what is described in 2015 (pg 58)
Response: We acknowledge the reviewer's comment. We have revised the conclusion in both the abstract and discussion as below.

In abstract
Conclusions: Enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation. With regards to the wide CI, we believe further studies are needed to confirm the efficacy of rehabilitation.

On page 22, line 365-369 in discussion
Taken together, the findings of the present meta-analysis indicate that enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation. With regards to the wide CI, we believe further studies are needed to confirm the efficacy of rehabilitation.

● the definition of enhanced physical rehabilitation (148-54) in many countries encompasses a normal rehabilitation pathway for all patients
Response: The contents of rehabilitation is not different between enhanced physical rehabilitation and standard care (a normal rehabilitation pathway). We defined enhanced physical rehabilitation as any protocoled rehabilitation following ICU discharge, designed to either commence earlier and/or be more intensive than the care received by the control group. To determine whether enhanced physical rehabilitation following ICU discharge improved clinically relevant outcomes, we excluded studies in which earlier and/or more intensive ICU physical rehabilitation (compared to the care received by the control group) was provided to patients in the intervention group.

● meta analysis described as first to focus on enhanced rehabilitation.....in which the study intervention was conducted only after ICU discharge however - half of the studies had rehabilitation within ICU before randomization
Response: We defined enhanced physical rehabilitation as any protocoled rehabilitation following ICU discharge, designed to either commence earlier and/or be more intensive than the care received by the control group. To determine whether enhanced physical rehabilitation following ICU discharge improved clinically relevant outcomes, we excluded studies in which earlier and/or more intensive ICU physical rehabilitation (compared to the care received by the control group) was provided to patients in the intervention group. Therefore, we excluded Morris's study (PMID: 27367766) which provided enhanced rehabilitation in ICU, and we did not exclude studies which provided the same rehabilitation program in ICU as standard care for both the intervention group and the control group (Jones et al., 2003; Cuthbertson et al., 2009; Connolly et al., 2015; Walsh et al., 2015; McWilliams et al., 2016). To confirm the effects of ICU rehabilitation as a normal rehabilitation pathway, we performed subgroup analysis for QOL and long-term mortality as shown figure A1, B1, C1 (ICU rehabilitation before randomisation ve No ICU rehabilitation before randomisation) in Online supplementary file 6.

According to reviewer's comment, we have revised the methods section as below (page 9-10, line 139-147)

Intervention was defined as any protocoled rehabilitation following ICU discharge, designed to either commence earlier and/or be more intensive than the care received by the control group. To determine whether enhanced physical rehabilitation following ICU discharge improved clinically relevant outcomes, we excluded studies in which earlier and/or more intensive ICU physical rehabilitation

(compared to the care received by the control group) was provided to patients in the intervention group. We excluded studies in which enhanced rehabilitation was provided in the ICU; however, we did not exclude studies in which the same rehabilitation program was provided in the ICU as standard care for both intervention group and control group.

● (292-4) ...'results ..... suggest that enhanced rehabilitation following ICU discharge could not improved QoL....' again a generalised conclusion for very limited data
Response: According to reviewer's suggestion, we have revised the manuscript as below (page 18, line 296-299)
The results of this up-to-date review covering 10 RCTs and 1110 patients suggest that enhanced rehabilitation following ICU discharge might not improve QOL or reduce short- or long-term mortality among patients who received mechanical ventilation at the 6 or 12 month follow-ups.

● (-305-7) unjustified conclusions -insufficient data , poor quality
Response: According to your suggestion, we have revised the manuscript as below (page 19, line 309-310)
Thus, neither enhanced rehabilitation in the ICU nor rehabilitation following ICU discharge appear to be superior to standard care in terms of QOL outcomes.

●(311-314) - early rehabilitation in other conditions has is some studies resulted in detrimental - it is can not be assumed transfer such conclusion to completely different cohorts is appropriate and the danger of doing this is not mentioned
Response: Thanks for the constructive comment. For this paragraph, we intended to mention comparisons with prior studies and possible explanations as to why our results were negative. We've revised the sentences to clarify our intention as follows: (page 19, line 315-320)

Specifically, intensive physical rehabilitation started within 48 hours of admission for exacerbations of chronic respiratory disease increased mortality at 12 months,[31] and higher-dose physical rehabilitation very early after stroke decreased favourable outcomes at 3 months.[32] Thus, implementation of an intensive rehabilitation program might not be indicated for all ICU survivors who received mechanical ventilation.

●(317-9) this review does not examine resource use or recuperation and therefore no conclusions can be taken form the analysis performed
Response: According to reviewer's suggestion, we deleted following sentences;
Though physical rehabilitation is relatively safe, it is labour intensive.[33] Our present findings do not support the allocation of additional resources to ensure intensive rehabilitation following ICU discharge, and rather indicate that physical rehabilitation staff resources might be better allocated to the management of non-severe patients such as those undergoing elective surgery and not requiring ICU admission.[34–36]

● ? for statistician - is sub-group analysis appropriate
Response: We carried out pre-specified subgroup analysis in PROSPERO [Taito et al]as recommended by the Cochrane Handbook.[Higgins et al.]

To reviewer #2

Thank you very much for the reviewer's thorough review of our manuscript. We have revised our manuscript according to the reviewer's suggestions. Our point-by-point responses to reviewer's comment are below.

This is a well presented and thorough manuscript. I have a few comments for consideration.
For the conclusion that physical rehab to have no patient centred effect to be secure we have to be

confident that the outcome measures are sensitive to change in this population and it is currently far from clear that this is the case- or that we really know hoe to do this. It is possible that the outcome measures are simply not sufficiently sophisticated enough- this should be acknowledged.
Several studies- the RECOVER and the PIX studies- did not demonstrate an improvement in primary quantitative outcome- but did show evidence of benefit of the intervention in parallel qualitative evaluation. This somewhat supports my first point.

Response: According to the reviewer's suggestion, the Associate Editor's comment, and reviewer #1's comments, we revised the conclusion in both the abstract and discussion as below.

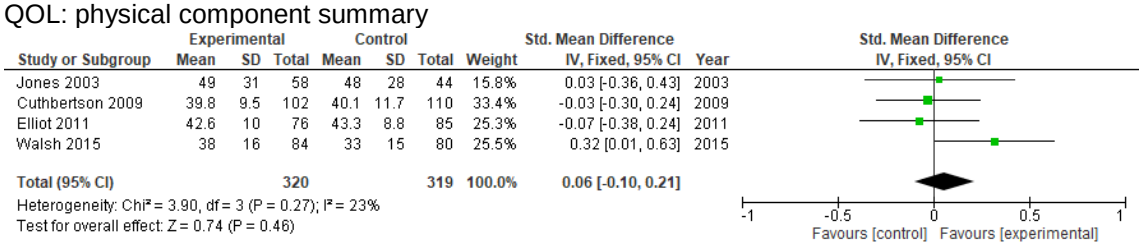
In abstract
Conclusions: Enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation. With regarda to the wide CI, we believe further studies are needed to confirm the efficacy of rehabilitation.

On page 22, line 365-369 in discussion
Taken together, the findings of the present meta-analysis indicate that enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation. With regard to the wide CI, we believe further studies are needed to confirm the efficacy of rehabilitation.

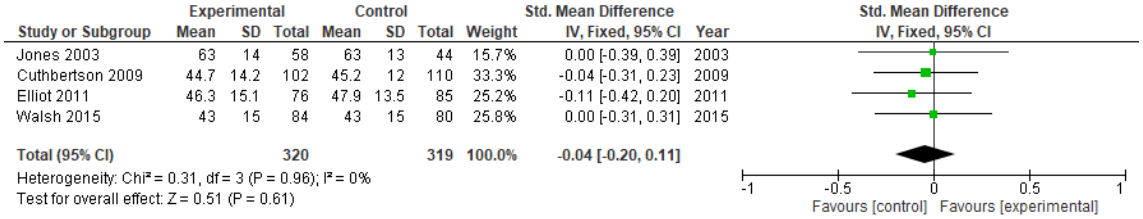
From work that we have done with patient and family groups they tell us that patient motivation and engagement is fundamental to full participation in the intervention- thus single modality physical interventions which ignore psychological aspects are very unlikely to be beneficial at a population level- although highly self-motivated individuals may derive benefit.
Response: We decided on the primary and secondary outcomes in our systematic review by considering the core outcome set [Major et al.]. We could not consider psychological aspects, and we could not perform subgroup analysis to confirm the effect on highly self-motivated individuals. According to the reviewer's suggestion, we have added these points to the discussion as below.(page 22, line 360-364)
Lastly, we could not consider psychological aspects in our review. However, effect of intervention for the general population is more clinically important than for that of highly self-motivated individuals, and we clarified that enhanced physical rehabilitation following ICU discharge may make little or no difference for the general population including highly self-motivated individuals.

The authors very sensibly chose a random effects approach to deal with statistical heterogeneity- but at a trial level there was heterogeneity in almost everything. It would be reasonable for them to emphasise the heterogeneity of outcome measures hinders overall analysis here- and somewhat erodes the power of the meta-analysis.
Response: According to the reviewer's suggestion, we performed sensitivity analysis for the primary outcomes using a fixed-effect instead of a random-effects model. The results were similar to the random effect model as shown below.

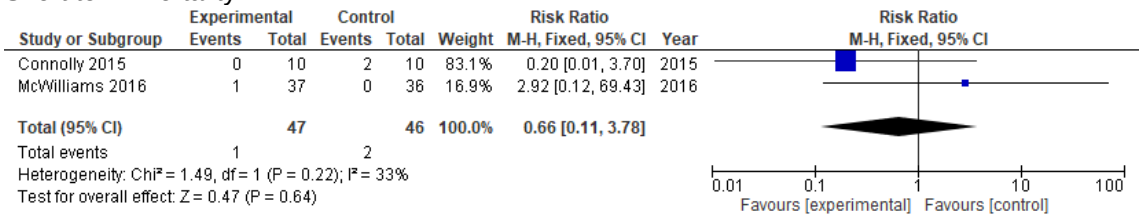
QOL: physical component summary



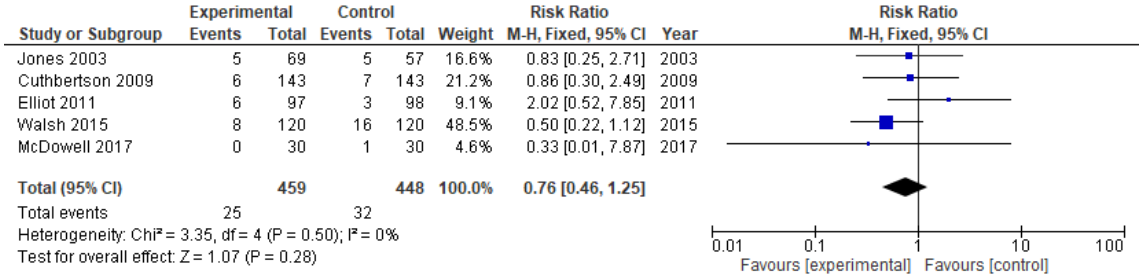
QOL: mental component summary



Short term mortality



Long term mortality



To reviewer #3

Thank you very much for the reviewer's thorough review of our manuscript. We have revised our manuscript according to the reviewer's suggestions. Our point-by-point responses to reviewer's comment are below.

The authors present the results of both a systematic review and meta-analysis on the effect of post critical care discharge rehabilitation on outcome. This topic has been previously addressed but the authors justify their study by the inclusion of new RCTs published since the previous systematic review of Connelly et al.
The study use standard Cochrane Collaboration methodology and appears well conducted. Pre-defined outcomes were chosen including Quality of life, ADL function and mortality. Comprehensive search strategies were employed supplemented by hand searching and in some cases personal contact with study authors. Search strategies are provided in one of the supplements. Study quality was assessed using standard risk of bias and GRADE assessment tools. Analysis was again standard using the Cochrane Review Manager software.
Ten RCTs were included. Results were presented using Forest plots for the meta analysis and descriptive statistics where appropriate. The conclusions were similar to previous publications with no strong evidence in favour of post ITU intensive physical rehabilitation. A mention of the very heterogeneous nature of the critical care populations included should be made.

Response: We agree with the reviewer's comments. Critical care populations are heterogenous. Therefore, we selected studies including only participants with an ICU stay of >48 hours during which mechanical ventilation was provided for at least 24 hours. On the other hand, the Cochrane review [Connolly, et al] included studies of adults who had been mechanically ventilated for 24 hours or longer and admitted to an ICU or critical care environment regardless of duration of stay in ICU.
According to the reviewer's suggestion, we have added this to the discussion as bellow. (page 21, line

346-349)

Fourth, ICU survivors have heterogeneous nature. To confirm the effect of enhanced physical rehabilitation for a particular group, we selected studies including only participants with an ICU stay of >48 hours during which mechanical ventilation was provided for at least 24 hours.

To reviewer #4

Thank you very much for the reviewer's thorough review of our manuscript. We have revised our manuscript according to the reviewer's suggestions. Our point-by-point responses to reviewer's comment are below.

1. Overall a well-written meta-analysis.
Response: Thank you very much for the reviewer's thorough review of our manuscript.

2. Mortality outcome: it is not clear what is meant by short-term and long-term mortality. Can you clarify this please? 30 days? 6 months? 1 year?
Response: We described that we divided the timing for the measurements of the outcomes into the short-term (28-35 days) and the long-term (6 months) in pre-specified protocol (PROSPERO registry ID: CRD42017080532).
According to the reviewer's suggestion, we have described the details of our outcomes in the manuscript in the materials and methods section as below.

We divided the timing for the measurements of the outcomes into the short-term (28-35 days) and the long-term (6 months). (page 10, line 158-159)

3. Also, for "long-term" mortality, journal articles often present hazard ratios, or log rank statistics and total number of deaths. Presenting RR for mortality suggests that the status of every patient is known at the time of assessment. This is rarely the case, as there is often a loss to follow-up (censoring) which must be accounted for. Could you please clarify your reasons for presenting long-term mortality effects in terms of RR?
Response: We thank the reviewer for their comment. As the reviewer pointed out the included study in our systematic review reported mortality as the total number of deaths at a particular time point with a certain proportion of loss to follow-up. However, no included study reported the death as a time to event data. Therefore, we synthesised the long term mortality as dichotomous data at clinically relevant time frame (long-term) with certain proportion of loss to follow-up (Jones 2003 (Intervention 8.7%, control 14.0%), Cuthbertson 2009 (Intervention 11.1%, control 10.5%), Elliot 2011(Intervention 13.4%, control 10.2%). Walsh 2015(Intervention 24.2%, control 21.7%), McDowell 2017(Intervention 26.7%, control 6.7%)). The total loss to follow-up in intervention were 15.7% and that of in control was 13.6%. As the reviewer pointed out, ideally the mortality outcomes should be reported as a time to event data. We have added this discussion to the discussion section as a future research implication. To consider attrition bias [Higgins et al.], we reassessed the risk of bias and changed the domain of incomplete outcome data from low to high in online supplemental file 5.

In discussion (page21, line 353-355)
Secondly, ideally the mortality outcomes should be reported as a time to event data, however, no included study reported the death as a time to event data. Further studies reporting as time to event data for mortality are needed.

4. Summary of findings: It would be clearer if the mortality endpoints had time durations, e.g. 30 day mortality or 1 year morality. Then the numbers (31 out of 1000) would be more meaningful to the reader.
Response: According to the reviewer's suggestion, we have revised the summary of findings table. We added "28-35 days" to short-term mortality and "6 months" to long-term mortality.

5. This reviewer noted that 9 of the 10 included studies reported HRQoL as an outcome measure. I assume different QoL instruments were used, but I wonder why the authors combine the study QoL results using a standardised mean difference, as they planned (see Statistical Analysis section)?
Response: We planned to divide the timing for the measurements of the primary outcomes into the short-term (28-35 days) and the long-term (6 months) in PROSPERO [Taito et al.]. 9 of the 10 included studies reported HRQoL as an outcome measure, and most of the measure was SF-36 score, but 4 studies reported outcomes in other timing such as 8 weeks and 3 months. In addition, we could not get enough information from author in one study to perform meta-analysis.
As per the reviewer's comments, we converted the median (inter quartile range) of SF-12 score to mean (standard deviation) in Walsh's study and we combined the study QOL results using a standardized mean difference as planned.
We re-analysed PCS and MCS of QOL score measuring SF-36 and SF-12 at 6 months as below.
We revised figure 2, table 1, supplementary online files 6.
We also revised manuscript as below.

In abstract
Regarding QOL, the SMD [95% CI] between the intervention and control groups regarding physical and mental component summary scores was 0.06 [-0.12 to 0.24] and -0.04 [-0.20 to 0.11], respectively.

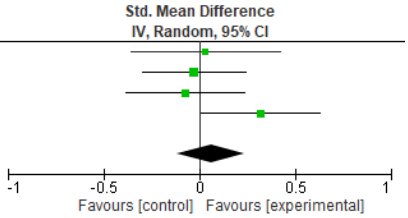
In results (page 16, line 254-257; page 16, line 260-262)
QOL was measured in 9 trials (see online supplementary file 3), but the short- and long-term QOL score were only available in 4 trials,[12, 22–24] whereas the other 5 trials measured these outcomes at a different time or had insufficient outcome data for meta-analysis.

The SMD between intervention and control regarding PCS and MCS scores measured by SF-36 or SF-12 characterizing QOL were 0.06 (95% CI, -0.12 to 0.24) and -0.04 (95% CI, -0.20 to 0.11), respectively (Fig. 2A and 2B, respectively).

2-A Quality of life: physical component summary (6 months)

	Experimental			Control				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Jones 2003	49	31	58	48	28	44	17.5%	0.03 [-0.36, 0.43]	2003
Cuthbertson 2009	39.8	9.5	102	40.1	11.7	110	31.3%	-0.03 [-0.30, 0.24]	2009
Elliot 2011	42.6	10	76	43.3	8.8	85	25.5%	-0.07 [-0.38, 0.24]	2011
Walsh 2015	38	16	84	33	15	80	25.7%	0.32 [0.01, 0.63]	2015
Total (95% CI)			**320**			**319**	**100.0%**	**0.06 [-0.12, 0.24]**	

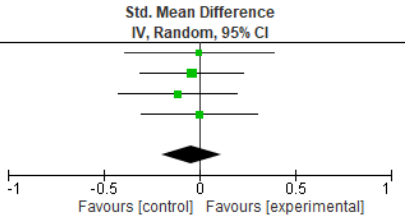
Heterogeneity: Tau² = 0.01; Chi² = 3.90, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 0.66 (P = 0.51)



2-B Quality of life: mental component summary (6 months)

	Experimental			Control				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Jones 2003	63	14	58	63	13	44	15.7%	0.00 [-0.39, 0.39]	2003
Cuthbertson 2009	44.7	14.2	102	45.2	12	110	33.3%	-0.04 [-0.31, 0.23]	2009
Elliot 2011	46.3	15.1	76	47.9	13.5	85	25.2%	-0.11 [-0.42, 0.20]	2011
Walsh 2015	43	15	84	43	15	80	25.8%	0.00 [-0.31, 0.31]	2015
Total (95% CI)			**320**			**319**	**100.0%**	**-0.04 [-0.20, 0.11]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 3 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)



VERSION 2 – REVIEW

REVIEWER	Rebecca Cusack Departments of Intensive Care University Hospital of Southampton NHS FT
REVIEW RETURNED	05-Mar-2019

GENERAL COMMENTS	6. Need to clearly identify specific outcome measures - rather than measures 'such as' and: duration of ventilation not described here 8. Reviews are on occasion used as point of referenced rather the primary work. Of the studies examined one was a feasibility study, and not RCT and therefore not powered for outcome measures. 15 English need minor editing The authors are congratulated on the rigorous methodology of this work. This is a very difficult area to address due to many confounding issues of patient heterogeneity, a question of appropriate outcomes in some of the studies (mortality) and differing follow times. None of the studies examined had significant outcomes ergo the result of this piece of excellent work is not surprising. As such I do not feel this paper contributes sufficiently to knowledge in this field.

REVIEWER	Professor Stephen Brett Imperial College London
REVIEW RETURNED	18-Feb-2019

GENERAL COMMENTS	These people have not properly addressed my comments. They seem very focussed on the statistical methods, rather than the human factors which generate the data and allow proper interpretation. My suggestions merely required them to acknowledge these issues in a little detail, and the limitations around interpretation which flow from them, in the Discussion. I think my comments were clear enough.

REVIEWER	Dr Simon Baudouin Royal Victoria Infirmary Newcastle upon Tyne NHS Foundation Trust United Kingdom
REVIEW RETURNED	26-Feb-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Teresa Neeman Australian National University, Australia
REVIEW RETURNED	17-Feb-2019

GENERAL COMMENTS	The authors have addressed all of my comments adequately.

VERSION 2 – AUTHOR RESPONSE

Point-by-point responses to the reviewer comments

Reviewer #1

Comment 1: Need to clearly identify specific outcome measures - rather than measures 'such as' and: duration of ventilation not described here
Response: We understand the reviewer's concern and agree that the main outcome measures should be listed explicitly. The outcomes considered in the present review were activity-of-daily-living function, quality of life, and mortality. These outcomes were listed in the pre-specified protocol of our study (PROSPERO registry ID: CRD42017080532).

While duration of ventilation is an important outcome in ICU patients, this variable did not enter in the present review as an outcome. Instead, the duration of mechanical ventilation in the ICU served as an inclusion criterion for our analysis (ventilation for >24 hours). We apologize that the previous version of the manuscript might have suggested otherwise.

We have clarified these aspects in the revised Abstract and Methods, as detailed below.

Revised Abstract:
"Objective: We aimed to determine whether enhanced physical rehabilitation following intensive care unit (ICU) discharge improves activities-of-daily-living function, quality of life (QOL), and mortality among patients who received mechanical ventilation in the ICU." (page 4, lines 43-46)

"Only adults who received mechanical ventilation for >24 hours were included." (page 4, lines 53-54)

Revised Methods:
"A recent systematic review by Connolly et al.[10] focused on randomised controlled trials (RCTs) regarding the effectiveness of enhanced exercise rehabilitation following ICU discharge in adult ICU survivors who had been mechanically ventilated for longer than 24 hours in the ICU. Despite the comprehensive search, this previous systematic review included only 6 RCTs with conflicting results, and no clear effect of the intervention on QOL, mortality, functional exercise capacity, or incidence of adverse events could be established at the time. Additionally, ADL, pain, return-to-work rate, muscle strength, and duration of delirium were not considered in that review.[10]" (pages 7-8, lines 101-108)

"The research question addressed in this study was: "Does enhanced physical rehabilitation following ICU discharge result in improved QOL, ADL function, and mortality (compared to those achievable with usual care) among patients who received mechanical ventilation in the ICU?'" (page 9, lines 126-129)

Comment 2: Reviews are on occasion used as point of referenced rather the primary work. Of the studies examined one was a feasibility study, and not RCT and therefore not powered for outcome measures.
Response: We thank the reviewer for this observation. Our meta-analysis indeed included two pilot RCTs: one by Salisbury et al. (single-centre pilot RCT; ref. #25), and one by Connolly et al. (two-centre pilot RCT; ref. #11). These pilot RCTs were included in the qualitative synthesis, as shown in online supplementary file 3.

Furthermore, we pooled the data from the pilot RCT by Connoly et al. (ref. #11) for analysis of short-term morality. This study, titled "Exercise-based rehabilitation after hospital discharge for survivors of critical illness with intensive care unit-acquired weakness: a pilot feasibility trial", is an RCT despite the misleading keyword "feasibility" used in the title. The methods for randomization used by Connolly et al. are described in their article as below (blue text).

"2.8. Randomization
Randomization was managed by the Mental Health and Neuroscience Clinical Trials Unit (London, UK) (see Online Supplement Section E1 for further detail). Treatment allocation was undertaken

independently of the research team. Once notified of treatment allocation by the Clinical Trials Unit, participants and relevant treating clinicians were informed. Because of the pilot status of the RCT and the nature of the therapy intervention, blinding of participants and the research team was not possible."

In our meta-analysis, we employed the GRADE approach to evaluate the certainty of the evidence including the effects of these small pilot RCTs because we believe that it is important to draw conclusions based on the best available evidence. We do not believe that we should exclude the two small RCTs because of small sample size (Dechartres et al., 2014).

Nevertheless, motivated by the reviewer's comment, we performed sensitivity analysis for short-term mortality after excluding the study by Connolly et al. The risk ratio [95% confidence interval] was 2.92 [0.12–69.43], which does not change the conclusion drawn before excluding the study of Connolly et al. (0.71 [0.05–9.80]). Therefore, we believe that our original judgement, as expressed in the pre-specified study protocol (PROSPERO registry ID: CRD42017080532), was appropriate.

References
Dechartres A, et al. Association between analytic strategy and estimates of treatment outcomes in meta-analyses. JAMA 2014;312:623-30.

Comment 3: English need minor editing
Response: We had our revised manuscript undergo proofreading by a professional language editor. We attach the certificate of English editing by Editage (http://www.editage.jp).

Comment 4: The authors are congratulated on the rigorous methodology of this work. This is a very difficult area to address due to many confounding issues of patient heterogeneity, a question of appropriate outcomes in some of the studies (mortality) and differing follow times. None of the studies examined had significant outcomes ergo the result of this piece of excellent work is not surprising. As such I do not feel this paper contributes sufficiently to knowledge in this field.
Response: We thank the reviewer for the kind comments and appreciation of our work, and agree that there are substantial limitations in the currently available literature in the field, which makes it difficult for clinicians and policy makers to make informed decisions. We have done our best to provide a relevant and up-to-date account of the available evidence by summarizing the findings of RCTs according to a pre-defined protocol for analysis and a standardized approach for evaluating the certainty of evidence. Therefore, while the conclusions might not be entirely surprising, the implications of our present findings are important not only for clinicians and policy makers but also for researchers who plan RCTs.

Motivated by the reviewer's comment, we expanded the Discussion to acknowledge the specific limitations pointed out by the reviewer.

Revised Discussion (page 22-23, lines 369-375)
"Lastly, the patient characteristics, follow-up timing, and types of outcomes reported might exhibit substantial heterogeneity not only across trials but also within each individual trial, an aspect we did not examine in the present analysis. However, upon reviewing the best available evidence based on a standardised approach, we confirmed that the direction of the effect and the effect size of enhanced post-ICU physical rehabilitation were similar in pooled studies, as reflected in the Forest plots (see details in online supplementary file 7)."

Reviewer #2

Comment 1: These people have not properly addressed my comments. They seem very focussed on the statistical methods, rather than the human factors which generate the data and allow proper interpretation. My suggestions merely required them to acknowledge these issues in a little detail, and the limitations around interpretation which flow from them, in the Discussion. I think my comments were clear enough.

Response: We apologize for not having adequately addressed the reviewer's previous comments and would like to assure the reviewer that we are fully committed to improving the manuscript as suggested. We had previously focussed only on the statistical methods rather than on the human factors simply because most studies do not report any data regarding human factors. In fact, most literature discussing the factors that may explain the lack of association in meta-analyses focus on clinical aspects. Clinical heterogeneity arises from differences in participant characteristics, intervention characteristics, and type or timing of outcome measurements (Higgings and Green, 2011). We believe that clinical heterogeneity is not the main factor explaining the lack of association noted in our meta-analysis. We discuss in detail below.

Participant characteristics

Clinical heterogeneity related to participant characteristics includes ethnic background, age, sex, baseline severity of the overall health status, and comorbidities (Gagnier et al., 2012) Of the seven studies pooled in our review, six were conducted in the UK, and none reported on the ethnic background of the participants. The mean or median age across the pooled studies is similar, as shown in the additional table (see below). Upon excluding the pilot RCT conducted by Connolly et al., the baseline physical status and sex do not differ substantially across the pooled studies. Although an observational study (Denehy et al., 2012) reported an association between the incidence of comorbidities and physical activity levels at 2 months from ICU discharge, no RCT reported data in this direction.

Regarding heterogeneity in terms of primary diagnosis, no RCTs reporting a positive effect of enhanced physical rehabilitation in patients who received mechanical ventilation in the ICU (Schweickert et al., 2009; Schaller et al., 2016) found any relationship with the nature of the disease. Nevertheless, a pilot RCT enrolling patients with sepsis reported that enhanced physical rehabilitation in the ICU improved QOL scores (Kayambu et al., 2015). Only two of the studies included in our meta-analysis (Walsh et al., 2015; McDowell et al., 2017) reported the primary diagnosis of participants, so it was not possible to examine this aspect in detail. However, we confirmed that the pooled studies did not show significant differences in outcomes and that the direction of the effect and the effect size of enhanced physical rehabilitation were similar across the pooled studies, as shown in the Forest plots (see online supplementary file 7 for details).

Additional table 1. Clinical heterogeneity in participant characteristics (intervention vs control)

Author, year, Country	Mean or median age, years	Baseline physical status (APACHE II score)	Sex (female)
Jones et al., 2003, UK	57 vs 59	17 vs 16	46.3% vs 42.1%
Cuthbertson et al., 2009, UK	59 vs 60	19 vs 19	40% vs 40%
Elliott et al., 2011, Australia	57.2 vs 57.5	19.5 vs 19.4	38% vs 39%
Connolly et al., 2015, UK	63.0 vs 68.5	24.5 vs 23.5	70% vs 70%
Walsh et al., 2015, UK	62 vs 62	20 vs 19	55.8% vs 58.0%
McWilliams et al., 2016, UK	55 vs 60.8	16.6 vs 15.9	32% vs 36%
McDowell et al., 2017, UK	51 vs 51	17.3 vs 15.2	57% vs 30%

Thus, we believe the impact of clinical heterogeneity arising from patient characteristics did not have a substantial impact on our conclusions.

Intervention characteristics

To investigate clinical heterogeneity arising from the nature and characteristics of the intervention, we carried out pre-specified subgroup analyses according to rehabilitation provision in the ICU, timing of commencement of the intervention, and intervention duration. We also planned subgroup analyses regarding the type of rehabilitation involved, treatment frequency, and type of control, but, unfortunately, we could not perform these analyses because the few studies included in the review

reported such data. As shown in online supplementary file 7, pre-specified subgroup analyses for the primary outcomes revealed no significant differences among sub-groups. Therefore, we believe that the effect of clinical heterogeneity of intervention characteristics did not impact our conclusions substantially.

Type or timing of outcome measurements

We decided the primary and secondary outcomes based on the core outcome set of rehabilitation after critical illness (Major et al., 2016). We classified the outcomes according to the timing of their measurement (short-term, at 28–35 days post-intervention; long-term, at 6 months post-intervention), per the provisions listed in the pre-specified protocol (PROSPERO registry ID: CRD42017080532). Short- and long-term data were not available in some included studies reporting QOL scores, ADL function, functional exercise capacity, and muscle strength. However, these studies did not report significant rehabilitation-associated improvement in such outcomes at different time points. Therefore, we believe that the effect of clinical heterogeneity arising from the type or timing of outcome measurements did not impact the conclusions substantially.

To conclude, we have done our best to provide a relevant and up-to-date account of the available evidence by summarizing the findings of RCTs according to a pre-defined protocol for analysis and a standardized approach for evaluating the certainty of evidence. Therefore, while the conclusions might not be entirely surprising and in consideration of the intrinsic limitations of available data, the implications of our present findings are important not only for clinicians and policy makers but also for researchers who plan RCTs.

Motivated by the reviewer's comment, we expanded the Discussion to acknowledge the specific limitations pointed out by the reviewer.

Revised Discussion (page 22-23, lines 369-375)
"Lastly, the patient characteristics, follow-up timing, and types of outcomes reported might exhibit substantial heterogeneity not only across trials but also within each individual trial, an aspect we did not examine in the present analysis. However, upon reviewing the best available evidence based on a standardised approach, we confirmed that the direction of the effect and the effect size of enhanced post-ICU physical rehabilitation were similar in pooled studies, as reflected in the Forest plots (see details in online supplementary file 7)."

References

- Denehy L, Berney S, Whitburn L, Edbrooke L. Quantifying physical activity levels of survivors of intensive care: a prospective observational study. Phys Ther 2012;92:1507-1517.
- Gagnier JJ, Moher D, Boon H, Beyene J, Bombardier C. Investigating clinical heterogeneity in systematic reviews: a methodologic review of guidance in the literature. BMC Med Res Methodol 2012;12:111.
- Higgins JPT, Green S (Eds). Cochrane handbook for systematic reviews of interventions, version 5.1.0. 2011. http://handbook-5-1.cochrane.org/ (accessed 24 May 2018).
- Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. Intensive Care Med 2015;41:865–874.
- McDowell K, O'Neill B, Blackwood B, et al. Effectiveness of an exercise programme on physical function in patients discharged from hospital following critical illness: a randomised controlled trial (the REVIVE trial). Thorax 2017;72:594–5.
- Schaller SJ, Anstey M, Blobner M, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet. 2016;388:1377-1388.
- Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373:1874-1882.
- Walsh TS, Salisbury LG, Merriweather JL, et al. Increased hospital-based physical rehabilitation and information provision after intensive care unit discharge: the RECOVER randomized clinical trial. JAMA Intern Med 2015;175:901–10.

Additionally, we would like to respond once more to the three points raised by the reviewer in the previous round

Previous comment 1: This is a well presented and thorough manuscript. I have a few comments for consideration.
For the conclusion that physical rehab to have no patient centred effect to be secure we have to be confident that the outcome measures are sensitive to change in this population and it is currently far from clear that this is the case- or that we really know hoe to do this. It is possible that the outcome measures are simply not sufficiently sophisticated enough- this should be acknowledged.
Several studies- the RECOVER and the PIX studies- did not demonstrate an improvement in primary quantitative outcome- but did show evidence of benefit of the intervention in parallel qualitative evaluation. This somewhat supports my first point.
Response: We thank the reviewer for this insightful comment. We have mentioned this aspect in the revised Discussion as below.

Revised Discussion (page 22, lines 360-363)
"Fourthly, the outcome measures might be not sufficiently sophisticated. For example, the RECOVER trial[15] did not demonstrate an improvement in the primary quantitative outcome, but showed evidence of benefit of the intervention in a parallel qualitative evaluation.[36]"

New reference
36. Ramsay P, Huby G, Merriweather J, et al. Patient and carer experience of hospital-based rehabilitation from intensive care to hospital discharge: mixed methods process evaluation of the RECOVER randomised clinical trial. BMJ Open 2016;6:e012041.

Previous comment 2: From work that we have done with patient and family groups they tell us that patient motivation and engagement is fundamental to full participation in the intervention- thus single modality physical interventions which ignore psychological aspects are very unlikely to be beneficial at a population level- although highly self-motivated individuals may derive benefit.
Response: We selected the primary and secondary outcomes based on the core outcome set (Major et al., 2016). While we fully agree with the reviewer that psychological aspects are very important to the success of rehabilitation, we could not consider psychological aspects in our review because few studies report such data. Therefore, we could not perform subgroup analysis to check the effect of high self-motivation.

References
Major ME, Kwakman R, Kho ME, et al. Surviving critical illness: what is next? An expert consensus statement on physical rehabilitation after hospital discharge. Crit Care 2016;20:354.

Motivated by the reviewer's comment, we expanded the Discussion as below.

Revised Discussion (page 22, lines 363-368)
"Fifthly, we could not consider the psychological aspects that are likely to affect the outcomes of rehabilitation. While our findings indicate a lack of benefit of enhanced post-ICU rehabilitation in the evaluated population, highly self-motivated individuals might have derived benefit from such therapies. Further studies should collect data on motivation and engagement, which are crucial in maximising the benefits of rehabilitation [37]."

New reference
37. Corner EJ, Murray EJ, Brett SJ. Qualitative, grounded theory exploration of patients' experience of early mobilisation, rehabilitation and recovery after critical illness. BMJ Open 2019;9:e026348.

Previous comment 3: The authors very sensibly chose a random effects approach to deal with statistical heterogeneity- but at a trial level there was heterogeneity in almost everything. It would be reasonable for them to emphasise the heterogeneity of outcome measures hinders overall analysis here- and somewhat erodes the power of the meta-analysis.
Response: We fully agree that there is substantial heterogeneity arising from differences in participant characteristics, intervention characteristics, and type or timing of outcome measurements.
Nevertheless, as discussed above, we believe that these clinical heterogeneities did not have a substantial impact on our conclusions. We are convinced that such a systematic review and meta-analysis is particularly important given the limitations of current literature in the field, which makes it

difficult for clinicians and policy makers to make informed decisions. We presented the best available evidence and employed a standard approach, which is also helpful for researchers planning RCTs in this field.

Motivated by the reviewer's comment, we expanded the Discussion to acknowledge limitations related to heterogeneity

Revised Discussion (page 22-23, lines 369-375):
"Lastly, the patient characteristics, follow-up timing, and types of outcomes reported might exhibit substantial heterogeneity not only across trials but also within each individual trial, an aspect we did not examine in the present analysis. However, upon reviewing the best available evidence based on a standardised approach, we confirmed that the direction of the effect and the effect size of enhanced post-ICU physical rehabilitation were similar in pooled studies, as reflected in the Forest plots (see details in online supplementary file 7)."

Reviewer #3

Comment: no further comments.
Response: We thank the reviewer for their thorough evaluation of our manuscript.

Reviewer #4

Comment: The authors have addressed all of my comments adequately.
Response: We thank the reviewer for their thorough evaluation of our manuscript.